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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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1912	7590	11/14/2005	EXAMINER	
AMSTER, ROTHSTEIN & EBENSTEIN LLP 90 PARK AVENUE NEW YORK, NY 10016			GROSS, CHRISTOPHER M	
			ART UNIT	PAPER NUMBER
			1639	
DATE MAILED: 11/14/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,804	VENEMA, F.	
	Examiner	Art Unit	
	Christopher M. Gross	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 8/11/2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 and 20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>4/5/2004, 5/9/2005</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, claims 1-13, 20; election of 3-aminotriethoxysilane in claim 7 and biomolecule elected as oligonucleotide in the reply filed on 8/11/2005 is acknowledged.

Claims 14-19, 21 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/11/2005.

Claims 1-13, 20 are examined herein.

Priority

2. This is a 35 USC 371 application which claims priority to PCT/EP00/07736 (8/9/2000) which claims priority to European Patent Application 99202649.2 (8/16/1999) in English. All priority papers have been received.

Abstract

3. The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, *apart from any other text*. The PCT face page does not qualify.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-13 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for adhering of 3-aminopropyltriethoxysilane onto aluminum oxide Anodics followed by adsorption of a biomolecule, the specification does not reasonably provide enablement for the other silanes with any other metal oxides in any form. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the relative skill of those in the art;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: The invention is drawn to a method of loading biomolecules to a aminosilanized metal oxide surface followed by subsequent removal of unloaded aminosilanes. Claim 1 and dependent claims 3-13, as well as claim 2 and dependent claim 20 are structured in such a way that they are broad in scope, not limiting the invention to one workable species of silane and one species of metal oxide.

(3 and 5) The state of the prior art and the level of predictability in the art: The behavior of silanes with metal oxides is often unpredictable. Bascom (1972 Macromolecules 5:792-798 entire document) points out the ease with which silane films can be washed off of metal surfaces. Halling et al (1979 Biotechnology and Bioengineering Vol XXI 393-416, entire document) on page 405 show the unexpected difference in retention (loss) of 3-aminopropyltriethoxysilane from two different metal oxides (Ni-TiO₂ versus Ni-Ni-O) upon washing with water.

Plueddemann (Silane Coupling Agents 2nd edition, 1991, pp 135-136) lists factors which play a roll in adhesion of silanes with metals including, the isoelectric point of the oxide, the ionic character of the oxide bond, solubility of the metal hydroxide in water, the presence or absence of chelators, and surface effects. Nevertheless, such factors are more useful for predicting the behavior of monoalkoxy silanes, since Plueddmann points out on page 63 that amino-trialkoxo silanes oligomerize upon dissolution in water.

The oligomerization represents a side reaction for strong adhesion to the metal oxide surface and is referred to as "vertical" polymerization. The competing alternative reactions of oligomerization vs. metal oxide adherence remain a challenge to

reproducibility in the art. A partial solution offered Krasnoslobodtsev et al (2002 Langmuir 18:3181-3184) was not available at the time the application was filed. Therefore in view of the above four references, the predictability in the art is low. There is no general protocol in the art for the *adhesion of silanes to metal oxides which guarantee the silane layer will not wash away*. Without the silane layer, the biomolecule cannot be loaded (claims 1-9, 13,20), attached (claim 11) or adsorbed (claim 10).

(4) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level or equivalent number of years experience. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6 and 7) The amount of direction provided by the inventor and the existence of working examples: The reaction of 3-aminopropyltriethoxy silane with aluminum oxide Anodiscs is well understood and characterized in the prior art. Applicant teaches an example using these two specific reagents. Absent from the specification, however are protocols using the other silanes listed in claim 7 in conjunction with other metal oxides.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: As the disclosed specification does not provide more extensive silanization protocols using other metals or silanes, the amount of experimentation necessary is substantial since reproducible and predictable silanization remains a challenge in the art. It is not evident that the silanization protocol presented in the specification would be successful with other silane plus metal oxide combinations. Therefore, it is deemed that further research of an unpredictable nature would be

necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, undue experimentation would be required of one of skill in the art to practice the full scope of the claimed invention.

5. Claims 1-13 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is lack of written description rejection.

The invention is broadly drawn to a method of loading biomolecules onto a aminosilanized metal oxide surface followed by subsequent removal of aminosilanes which are not loaded with biomolecules.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116).

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics

Art Unit: 1639

coupled with a known or disclosed correlation between function and structure; or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly* 119 F.3d at 1568. 43 USPQ2d at 1406.

With the exception of the combination of adhering of 3-aminopropyltriethoxysilane onto aluminum oxide Anodics, the skilled artisan cannot envision a protocol which would lead to a durable (i.e. hydrolytically stable) silane layer on other metal oxides. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the technique.

Therefore, only the combination of 3-aminotriethoxysilane with aluminum oxide Anodics, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 each recite the limitation "loading the support" in step (b). There is insufficient antecedent basis for this limitation in the claim.

Claims 1 and 2 each recite the limitation "treating said loaded support" in step (c). There is insufficient antecedent basis for this limitation in the claim.

Claim 12 recites vague and indefinite language as to different spots that may be the same or different. It is not clear as to what exactly (e.g. chemical structure, biological activity, physical property) is the same or different and whether the spots or the biomolecules differ. As currently written, the scope of the claim unascertainable.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In each claim 1 and 2, the omitted steps are: after which step are the unloaded amino groups removed from the silanating agent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Groman et al (US Patent 4827945).

The claimed invention comprises three steps: (a) activating a [metal oxide] surface of the support by means of a silanating agent comprising an amine group; (b) loading the support by attaching biomolecules to the activated surface; (c) treating said loaded support with an [aqueous] acidic (claim 1) or neutral (claim 2) or alkaline (claim 2) solution.

The preamble of claims 1 and 2 states, "for removing non-loaded amino groups which form part of the silanating agent. " Generally, no patentable weight is accorded to the preamble where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Groman, et al throughout the document and especially column 16-17 teach activation of iron oxide with the silane N-2-aminoethyl-3-aminopropyltrimethoxysilane reading on step (a) of each claim 1 and 2. Groman et al disclose adsorbing various biomolecules including antibodies, carbohydrates, hormones, and neural transmitters in the table at column 20, reading on step (b) of each claim 1 and 2. Groman et al disclose hydrolysis [which can be either acid or base catalyzed], as a means of removing excess silane in column 17 reading on treatment step (c) of each claim 1 and 2.

8. Claims 1-3, 8, 9, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Weetall (Methods in Enzymology 44:143-148).

The claimed invention comprises three steps: (a) activating a [metal oxide] surface of the support by means of a silanating agent comprising an amine group (defined as 3-aminopropyltriethoxysilane in claims 8 and 9); (b) loading the support by attaching biomolecules to the activated surface; (c) treating said loaded support with an [aqueous] acidic (claim 1) solution at pH 2-6 (claim 3), or neutral (claim 2) or alkaline (claim 2) solution at pH 6-7 (claim 20).

Weethall, throughout the document and especially pp 139 and Table I teaches aminosilanization of various metal oxides with 3-aminopropyltriethoxysilane reading on step (a) of each claim 1 and 2 as well as claims 8 and 9. Weethall immobilizes enzymes, reading on step (b) of each claim 1 and 2. Weethall discloses treating the metal oxides with hydrochloric acid until the pH is between 3 and 4, reading on claims 1 and 3. Weethall also discloses treating other silanized metal oxides at pH 4.5, pH 7 and pH 10 reading on treatment step (c) of each claim 1 and 2 and claim 20.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 1-13 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Groman et al** (US Patent 4827945) and **Van Damme et al** (WIPO 99/02266 – IDS Entry 4/5/2004) .

Groman, et al throughout the document and especially column 16-17 teach activation of iron oxide with the silane N-2-aminoethyl-3-aminopropyltrimethoxysilane. Groman teach adsorbing various biomolecules. Groman et al teach hydrolysis, as a means of removing excess silane.

Groman et al does not teach using 3-aminopropyltriethoxysilane (the elected species), however.

Van Damme teach, throughout the publication and especially on page 10, immobilization of an oligonucleotide using 3-aminopropyltriethoxysilane on Anodiscs.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made, to utilize the silane employed by Van Damme et al with the hydrolysis method of Groman et al.

In addition to N-2-aminoethyl-3-aminopropyltrimethoxysilane, Groman et al disclose, the entire class of polymerizable aminosilanes as workable and that would have motivated one of ordinary skill in the art to try other aminosilanes known in the art.

One of ordinary skill could do so with a reasonable expectation of success given the successful examples presented by Van Damme et al.

Conclusion

10. Claims 1-13 and 20 are not allowed.

Art Unit: 1639

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Gross whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher M Gross
Examiner
Art Unit 1639


PADMASHRI PONNALURI
PRIMARY EXAMINER

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